REMARKS

Claims 1-19 and 22-28 are currently pending in the present application. Claims 2 and 13 have been amended to clarify that the dose comprises a daily dose of strontium of at least about 0.01 g. Also, claim 25 has been amended to correct a typographical error. Lastly, claim 27 has been amended to delete the trademarks/trade names recited in this claim.

New claims 29-32 have been added. Support for these new claims appear in paragraph [0038] and orginal claim 19. No new matter is believed to be introduced by these amendments and new claims.

Upon entry of these amendments, claims 1-19 and 22-32 will be pending.

I. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

In the Office Action, the Examiner has rejected claim 27 under 35 U.S.C. § 112, second paragraph as allegedly having uncertain claim scope because claim 27 contains the following trademarks/trade names Sustiva®, Retrovir®, Epivir®, Ziagen®, Hivid®, Videx®, Zerit®, Viread®, Emtriva®, Lexiva®, Viramune®, Rescriptor®, Fuzeon®, Invirase®, Fortovase®, Norvir®, Crixivan®, Reyataz®, Viracept®, and Agenerase®. Applicants wish to point out that claim 27 recites the names of the anti-retroviral compounds and that the respective trademarks/trade names for these compounds are placed in parentheticals next to the names of the compounds. Therefore, a person of ordinary skill in the art would be aware of the anti-retroviral compounds that are being claimed and the trademarks/trade names do not render claim 27 uncertain in scope. Nevertheless, solely to expedite the prosecution of the present application, Applicants have deleted the trademarks/trade names recited in claim 27. Applicants reserve the right to prosecute any deleted subject matter in one or more continuing patent applications.

Applicants submit that the rejection is now moot and should be withdrawn.

II. REJECTION UNDER 35 U.S.C. § 103(a)

On pages 2-4 of the Office Action, the Examiner has rejected claims 1-28[1] under 35 U.S.C. § 103(a) as being unpatentable over Little et al., International Application Publication

[1] Claims 20 and 21 were canceled prior to the date of the Office Action.

No. WO 02/062351 A1 published August 15, 2002 ("Little") in view of Marie *et al.*, "Mechanism of Action and Therapeutic Potential of Strontium in Bone," published August 8, 2001 ("Marie"). Applicants respectfully disagree with this rejection.

A. Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). In its decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 550 U.S. at 406-407 (quoting *Graham*, 383 U.S. at 17-18). The Supreme Court also held that:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does*. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR, 550 U.S. at 418-419 (emphasis added).

B. The Claims Are Not Obvious Based on Little in View of Marie

Claims 1-6, 17-19 and 24, as well as new claim 29, are directed to a method for the treatment and/or prophylaxis of an osteonecrotic bone disease in a mammal in need thereof comprising the administration a strontium-containing compound. Claims 7-16 and 25-27, as well as new claim 30, are directed to a method for the treatment and/or prophylaxis of an

osteonecrotic bone disease, in a mammal who is to be or is treated with a therapeutic agent known to or suspected of inducing apoptosis and/or necrosis of bone cells, the method comprising administering a strontium-containing compound in combination with the therapeutic agent. Claims 22 and 28, as well as new claim 31, are directed a composition, and claim 23 and new claim 32 are directed to a kit, in which the composition or kit comprises a strontium-containing compound and a therapeutic agent known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone disease.

In osteonecrotic bone diseases, the necrosis or death of bone cells occur. The bone cell death occurs generally as a result of a temporary or permanent loss of blood flow to the bone. The death of the bone cells causes the bone to collapse. [2]

As noted in the present specification, osteonecrotic bone diseases, such as osteonecrosis, are distinct from osteoporosis. (Specification at ¶ [0009].) In contrast to osteonecrotic bone diseases, osteoporosis does not involve the death of bone cells. Instead, osteoporosis results from the weakening of bone that makes them prone to fracture. Specifically, as people age, they begin to gradually lose bone strength because the balance between bone resorption and bone formation shifts so that the pace of new bone formation cannot keep up with the bone resorption or bone loss. As a result, bones become thinner and structurally weaker.[3] Therefore, osteonecrotic bone diseases, such as osteonecrosis, and osteoporosis arise from significantly different causes. Thus, osteonecrotic bone diseases and osteoporosis are distinct and significantly different medical conditions.

In the Office Action, the Examiner relies on Little and Marie to allege that it would have been obvious to one of ordinary skill in the art to use strontium ranelate, a strontium-containing compound, in the treatment of osteonecrosis. (Office Action at 4.) Specifically, the Examiner states that Little teaches the treatment and prevention of osteonecrosis by the administration of

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[2] *See* About.com: Rheumatoid Arthritis/Joint Conditions - What Is Osteonecrosis? from http://arthritis.about.com/b/2010/05/09/what-is-osteonecrosis.htm?p=1, which is attached hereto as Appendix 1 and included in the Information Disclosure Statement concurrently submitted herewith.

[3] *See* About.com: Orthopedics - What You Need to Know About Osteoporosis from http://orthopedics.about.com/od/osteoporosis/tp/osteoporosis.htm?p=1, which is attached hereto as Appendix 2 and included in the Information Disclosure Statement concurrently submitted herewith.

bisphosphonates. (*Id.* at 3.) Also, the Examiner states that Little teaches that the application of therapeutically effective amounts of bisphosphonates will slow the resorption and collapse of necrotic bone as well as promote increased mineral content of the necrotic bone. (*Id.*) The Examiner acknowledges that Little "lacks a teaching wherein the composition comprises a strontium-containing compound." (*Id.* at 4.) To remedy this absence of a strontium-containing compound in Little, the Examiner relies on Marie, which the Examiner asserts as teaching the use of strontium ranelate to increase bone formation and reduce bone resorption. (*Id.*) The Examiner then concludes that since Little and Marie teach that both bisphosphonates and strontium ranelate act by increasing bone formation and reducing bone resorption, "it would have been obvious [to] one ordinary skill in the art that strontium ranelate would also be useful in the treatment of necrosis." (*Id.*) Applicants respectfully disagree with the rejection.

Neither Little nor Marie discloses using a strontium-containing compound for the treatment and/or prophylaxis of an osteonecrotic bone disease in a mammal. Moreover, neither reference provides any reason to modify their respective teachings to arrive at a method for the treatment and/or prophylaxis of an osteonecrotic bone disease using a strontium-containing compound.

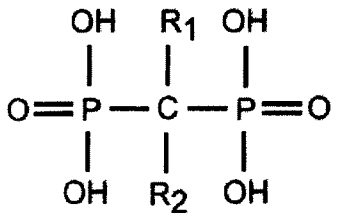
Little discloses the use of bisphosphonates for the treatment of osteonecrosis. (*See* Little at abstract.) In particular, Little describes the use of bisphosphonates, which include zoledronic acid or zoledronate as well as pamidronate, for treating osteonecrosis. (*Id.* at 6 and 10.) Also, Little describes test results from an animal study in which rats with necrotic bone were administered zoledronic acid. (*Id.* at 15-19.) Little states that administration of this bisphosphanate resulted in complete revascularisation and preservation of bone architecture, as well as reduced epiphyseal destruction but also allowed new bone formation and mineralisation leading to a viable, preserved epiphysis. (*Id.* at 18-19.)

As the Examiner acknowledged in the Office Action, Little fails to teach the use of a strontium-containing compound. (Office Action at 4.) Thus, Little does not disclose the use of a strontium-containing compound for treating osteonecrosis. In fact, Little does not even mention the use of any compound other than a bisphosphonate to treat osteonecrosis.

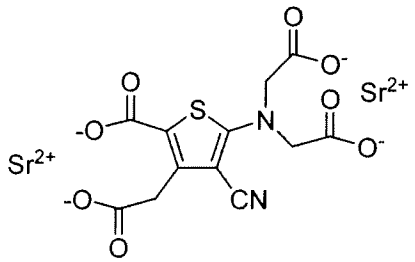
Moreover, Little also does not provide, and the Examiner does not point to, a reason or suggestion to modify Little's disclosure of the use of bisphosphonates to treat osteonecrosis.

Little teaches that its use of bisphosphonates achieves its intended purpose of treating osteonecrosis. By disclosing that bisphosphonates achieve this intended purpose and failing to suggest any other compounds for treating osteonecrosis, Little fails to provide a person of ordinary skill in the art with any motivation to use a compound other than a bisphosphonate for treating osteonecrosis. Furthermore, in view of the fact that (1) osteonecrosis and osteoporosis are significantly different medical conditions and (2) Little does not teach that any compound other than bisphosphonate should be used to treat osteonecrosis, the person of ordinary skill in the art would not have any reasonable expectation that strontium ranelate, which Marie teaches as a potential treatment for osteoporosis, could be used to treat osteonecrosis. Accordingly, the person of ordinary skill in the art would not have been motivated to modify the teachings of Little by substituting the strontium ranelate disclosed in Marie for Little's bisphosphonates to treat osteonecrosis

In addition, the chemical structures of the bisphosphonates disclosed in Little and that of strontium ranelate are significantly different. Set forth below is Fig. 1 from Little, which Little describes as showing the formula of bisphosphonates useful for treating osteonecrosis. Little discloses that R_1 and R_2 are varied to give various potencies and other properties to the bisphosphonate. (*Id.* at 14.) Also shown below is the chemical structure of strontium ranelate, which is significantly different from the chemical structure of Little's bisphosphonates.



Little's bisphosphonates in Fig. 1



strontium ranelate

For example, as shown in the above figures, unlike Little's bisphosphonates, strontium ranelate does not include any phosphonate group. In view of the differences between their chemical structures, the person of ordinary skill in the art would not have been motivated to substitute

Marie's strontium ranelate for Little's bisphosphonates. Therefore, the person of ordinary skill in the art would not have been motivated to modify the teachings of Little by substituting the strontium ranelate disclosed in Marie for the bisphosphonates disclosed in Little to treat osteonecrosis.

Marie also does not disclose using a strontium-containing compound for the treatment and/or prophylaxis of an osteonecrotic bone disease. In fact, Marie does not even mention osteonecrotic bone diseases, let alone any method for their treatment and/or prophylaxis. Instead, Marie discloses that strontium ranelate may be potentially useful for the treatment of osteoporosis and osteopenic disorders related to osteoporosis. (*See* Marie at 125.) Marie does not disclose that its strontium ranelate can be used to treat conditions other than osteoporosis and related osteopenic disorders. Thus, Marie does not provide any disclosure of using a strontium-containing compound for the treatment and/or prophylaxis of an osteonecrotic bone disease.

Furthermore, the person of ordinary skill in the art would not be motivated to use strontium ranelate, which Marie teaches for treating osteoporosis, for the treatment and/or prophylaxis of osteonecrotic bone diseases. As discussed above, osteonecrotic bone diseases and osteoporosis are signficantly different medical conditions. In particular, osteonecrotic bone diseases, such as osteonecrosis, and osteoporosis arise from significantly different causes. Osteonecrosis results from the death of bone cells due to a lack of sufficient blood supply to the bone. In contrast, osteoporosis results from the gradually lose of bone strength because the balance between bone resorption and bone formation shifts so that the pace of new bone formation cannot keep up with the bone resorption or bone loss. Therefore, since osteonecrosis and osteoporosis are different medical conditions, the skilled artisan would not have a reasonable expectation that a compound that could be useful for treating osteoporosis, such as Marie's strontium ranelate, would be effective in the treatment and/or prophylaxis of an osteonecrotic bone disease, such as osteonecrosis.

Thus, neither Little nor Marie discloses the use of a strontium-containing compound for the treatment and/or prophylaxis of an osteonecrotic bone disease. In addition, neither of these references provides any reason to modify its teachings to use a strontium-containing compound for the treatment and/or prophylaxis of an osteonecrotic bone disease. Accordingly, the rejection of the claims based on the combination of Little and Marie is improper.

It is respectfully submitted that the Examiner has simply taken two isolated references, each directed to distinct medical conditions and unrelated compounds, that disclose elements of the pending claims and combined the references when there would be no reason or motivation for a person of ordinary skill in the art to do so. The Examiner has impermissibly used the Applicants' disclosure and hindsight to find a reason to combine Little and Marie where no other reason to combine them exists. *KSR*, 550 U.S. at 421 (cautioning against reading the Applicant's disclosure of the claimed invention at issue into the prior art and upholding the principle of avoiding the use of hindsight reconstruction); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987) (noting that using hindsight reconstruction to pick and choose among isolated disclosures in the prior art to render the claims obvious should be avoided).

Accordingly, Applicants request that the rejection of the pending claims as being unpatentable over Little and Marie under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

As all rejections are believed to be overcome and all claims are believed to be in condition for allowance. An early notice to that effect would be appreciated. Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: November 23, 2010

For: Thomas G. Rowan (Reg. No. 34,419)

By: Catharina J. Chin Eng (Reg. No. 42,412)

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Enclosures

APPENDIX 1

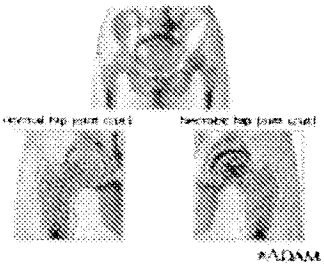
About.com: Rheumatoid Arthritis / Joint Conditions
Arthritis Blog

By Carol Eustice, About.com Guide

About.com Health's Disease and Condition content is reviewed by the Medical Review Board

What Is Osteonecrosis?

Sunday May 9, 2010



Osteonecrosis[1], also known as avascular necrosis, aseptic necrosis and ischemic bone necrosis, is a condition that develops as a consequence of temporary or permanent loss of blood supply to bone. The lack of blood supply to bone causes that part of the bone to die. The bone may collapse as it dies, and if the affected bone is near a joint, the joint surface can collapse.

The American Academy of Orthopaedic Surgeons estimates that 10,000 to 20,000 people develop osteonecrosis each year. Learn more about the cause, symptoms, and treatment in What Is Osteonecrosis?[2]

Related Resources:

- Guide to Osteonecrosis[3]
- More About Osteonecrosis[4]
- Bone Pain and Tenderness[5]
- The Facts of Corticosteroids[6]
- Osteonecrosis of the Jaw Tied to Bisphosphonates[7]

Join the Discussion:

- Join Us in Our Arthritis Forum / Message Board[8]

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6. http://arthritis.about.com/cs/steroids/a/corticosteroids.htm

7. http://arthritis.about.com/b/2009/01/10/arthritis-patients-should-be-aware-of-complication-tied-to-bisphosphonate-use.htm
8. http://arthritis.about.com/mpboards.htm
9. http://arthritis.about.com/b/2010/05/09/what-is-osteonecrosis.htm?p=1#gB3
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12. http://arthritis.about.com/b/2010/05/09/coccyx-cushion-helps-relieve-lower-back-pain.htm
13. http://arthritis.about.com/b/2010/05/13/tiger-woods-facet-joint-inflammation-causing-neck-pain.htm
14. http://arthritis.about.com/b/2010/05/09/what-is-osteonecrosis.htm?p=1#commentform

APPENDIX 2

About.com: Orthopedics

What You Need to Know About Osteoporosis

By Jonathan Cluett, M.D., About.com Guide *Updated June 19, 2009*

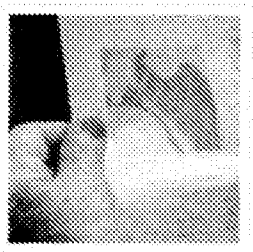
About.com Health's Disease and Condition content is reviewed by the Medical Review Board

Osteoporosis is a condition that causes weakening of the bones in your body. Also called "brittle bone disease," osteoporosis increases your chance of sustaining a broken bone. Broken bones can cause significant problems, especially when a spine fracture or broken hip occurs. Because of these concerns, all people should understand their chance of developing osteoporosis, and if they need steps to prevent the development or progression of osteoporosis.

What is Osteoporosis?[1]

Osteoporosis is a condition that weakens the bones of your skeleton. Bones, like other tissues in your body, are living structures that constantly are changing. New bone is made and old bone is taken away. Osteoporosis develops when the pace of new bone formation cannot keep up with the loss of bone.

How is Osteoporosis Diagnosed?[2]



3

Photo © Constantinos Gerakis

Everyone should know their risks for developing osteoporosis, and anyone who is "at risk[4]" for osteoporosis should have their bone density checked. A bone density test[5] can be performed for patients who may have osteoporosis. Bone density tests are also useful to monitor the progression of osteoporosis and the response to treatments.

When Should I Be Tested?[6]

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Photo © Sheryl Griffin

Some people should be tested for osteoporosis at an earlier age. Knowing the signs to look for can help you understand when the time is right to have a bone density test. If you are ever unsure, you should discuss this with your doctor. It is also a good idea to ask your doctor about a bone density test. Your doctor may be focused on management of your blood pressure, cholesterol, or other medical conditions. It is helpful if you ask about when to have a bone density test[8].

Warning Signs & Symptoms[9]

Osteoporosis is a condition that causes thin and weak bone. Preventing the progression of osteoporosis can help reduce the risk of fracturing the bone. Know the warning signs that you may have osteoporosis, so you can get help preventing the progression of this condition.

Osteoporosis Drugs[10]

Medications are often used as part of the treatment for patients with osteoporosis, as

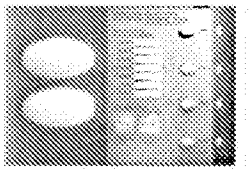

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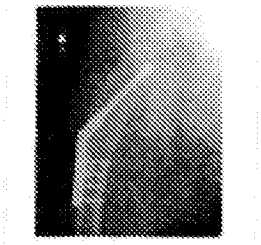
Photo © Gold Standard

well as those who have a significant chance of developing osteoporosis. Most osteoporosis medications try to prevent our natural process of bone loss. A new type of medication is also being used in some situations to stimulate bone formation.

Osteoporosis & Fractures



12

Photo © Jonathan Cluett, M.D.

Broken bones are the often the end result of osteoporosis. The goal of treatment is to prevent sustaining a broken bone, especially a broken hip. Some of the more commonly fractured bones in the body as a result of osteoporosis include:

- Wrist Fractures[13]
- Spine Compression Fractures[14]
- Shoulder Fractures[15]
- Pelvis Fractures[16]
- Hip Fractures[17]
- Tibial Plateau Fractures[18]
- Ankle Fractures[19]

Any broken bone can be the result of osteoporosis. These are the more common injuries seen with this condition.

Prevention of Fractures[20]

The problem with osteoporosis is that this condition increases your chance of sustaining a fracture. Fortunately, there are steps you can take to prevent these injuries. Most osteoporosis related fractures occur as the result of simple injuries and falls around the house. Taking steps to improve your bone health helps to prevent fractures. Other steps you can take include checking medications for side-effects that can lead to falls, and having your vision regularly evaluated.

Links in this article:

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